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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,900	05/26/2000	John P. Carulli	032796-019	8399

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,900	CARULLI ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7 and 48-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7 and 48-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 8/23/2005. The amendment filed 7/19/2005is acknowledged and has been entered. Claims 1, 2, 6, 7, 48-67 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7 and 67 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the candidate molecule" in the last line of the claim. However, the claim was amended to delete the recitation "candidate molecule" from the claim. Therefore, there is insufficient antecedent basis for this limitation in the claim. It is noted that amending the claim such that "the candidate molecule" is changed to "the reagent that modulates a lipid" would obviate this rejection. It is respectfully pointed out that claim 7 also includes the limitation "the candidate molecule". Furthermore, claims 7 and 67 depend on claim 6 and are therefore rejected for the same reason.

Claim Rejections - 35 USC § 101 and 112, 1st paragraph combined

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 6, 7 and 48-67 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility, for the reasons of record as set forth in the Office Action mailed 2/24/05.

Claims 1, 2, 6, 7 and 48-67 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for the reasons of record as set forth in the Office Action mailed 2/24/05.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In addition, and separate from the rejections above, claims 1, 2, 6, 7 and 48-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record as set forth in the Office Action mailed 2/24/05.

Response to Arguments

Applicant's arguments filed 8/23/2005 have been fully considered but they are not persuasive.

With respect to the rejection of claims under 35 USC 101, Applicants contend that the threshold of utility is not high. Applicants also refer to the "Utility Guidelines" and emphasize that the Guidelines state that the examiner's decision must be supported by a preponderance of all the evidence of record, and that the asserted utility must be accepted unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. Applicants assert that the Office improperly rendered its conclusion by not applying the evidentiary standard, it takes a **preponderance of evidence** to mete out a rejection based on lack of utility (Emphasis by Applicants). Applicants contend that the Office has not considered the each of the pieces of evidence as a whole, and argue that the asserted utility is strongly supported by the combination of the evidence as a whole. Applicants assert that they have shown that Zmax1 and HBM are members of the lipid receptor protein family and further assert that Zmax1 and HBM have been shown to have a role in lipid regulation. Applicants assert that they have provided experimental data of an altered lipid profile in extended kindred with the HBM phenotype and assert that

features of the Zmax1/HBM gene and its relationship to a family of receptors in disease conditions are discussed in the specification. Applicants contend that because lipid regulation is not limited to a single process but encompasses many different processes there is an automatic conclusion that the claimed method lacks utility. Applicants assert that the Office has not demonstrated a prima facie case of lack of utility. Applicants indicate that the Office is asserting a new utility standard that requires a complete explanation of the working model that forms the scientific basis of the claimed invention, and that the new standard applied by the Office is improper. Applicants also assert that methods of screening are described as having a specific and unquestionable substantial utility. Applicants argue that HBM is merely a single amino acid different from Zmax1 and further assert that HBM and Zmax1 are involved in the same signaling cascade and that only the biological activity of the protein has been changed. Applicants assert that Example 3 demonstrates that the HBM variant when expressed in humans is correlated to an altered lipid profile and contend that the skilled artisan could correlate the observed phenotype to a function of Zmax1 caused by the HBM polymorphism. Applicants argue that since the claimed methods should be determined to have a specific and substantial, if not well established utility, then the methods would also be enabled.

In response, Applicants arguments have been fully considered, but are not persuasive. It is acknowledged that it takes a preponderance of evidence to mete out a rejection based on a lack of utility. However, the Examiner respectfully disagrees with the Applicants that each piece of evidence has not been considered as a whole. All cited references have been fully considered. It is respectfully pointed out that the utility rejection is based on the finding that the instant claims

are not supported by a substantial and specific asserted utility nor is there a well-established utility for the claimed methods.

The instant claims are drawn to a method of identifying a reagent that "modulates a lipid". This is in contrast to the previous claims which were drawn to a method for identifying a molecule involved in lipid regulation. It was previously indicated that the term "involved" in the previous claims was vague and did not indicate how the molecule was involved in lipid regulation. In the instant case, although the term "involved" has been deleted from the claims, identifying a reagent that "modulates" a lipid still does not have a specific and substantial utility because further experimentation would be required. That is, completing the claimed method would result in the identification of a reagent that presumably "modulates" a lipid; however, without any indication what "modulates" encompasses (and without an indication of which lipid the reagent modulates), further experimentation would be required in order to determine a "real world" use for the identified reagent.

Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use for the claimed method. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Therefore, the assertion that Zmax1 and HBM are members of the lipid receptor family of proteins, even in view of the cited art, does not establish a substantial or real-world use for the claimed method because once the method is completed additional experimentation would be required. Thus, the present disclosure is only a starting point for further research and investigation into potential practical uses of the

claimed polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Therefore, the utility of an invention must be in readily available form. In Brenner v. Manson, 148 USPQ 689 (Sup. Ct. 1966) a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in USC 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. In the instant case, although the claimed method may be "useful" given its broadest interpretation, the claimed invention does not have an immediately obvious or fully disclosed "real world" utility because further experimentation would be required to determine which lipid is modulated by the compound and to determine the actual modulation caused by the reagent.

Furthermore, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (MPEP 2107.01). This is the case with the instant method where the claims of identifying a reagent that modulates

a lipid, without any indication "modulates" encompasses or even which lipids the reagent would "modulate" do not fully disclose a "real world" utility.

It is also respectfully pointed out that MPEP 2107.01(c) indicates that a method of assaying for or identifying a material that itself has no specific and/or substantial utility does not constitute a substantial utility. In the instant case, the claims encompass a method for identifying a material that "modulates a lipid". However, since "modulating a lipid" is not a specific and substantial utility the claimed method does not have a specific and substantial utility, either.

It is acknowledged that the applicants have asserted that the HBM and Zmax1 proteins are members of the LDL receptor family of proteins. However, as previously indicated, simply because a protein may happen to be an LDL receptor is no indicative of any particular function for the protein (or any reagent that interacts with it), as the prior art recognizes that lipid receptors can have a plethora of different functions in a cell. However, the specification and the art of record do not indicate any particular function for the Zmax1 and HBM proteins. Therefore, at best, the specification has merely identified Zmax1 and HBM, in general, as being lipid receptors without identifying how they are involved in modulating lipids. Therefore, using Zmax1 and HBM in methods of identifying reagents that modulate a lipid are not specific because any member of the lipid receptor family could be used to identify a reagent that "modulates" a lipid.

The specification and relevant art do not disclose any "well-established" utilities for using Zmax1 and/or HBM in a method of identifying reagents that modulate a lipid.

In response to Applicants assertion that the Office is asserting a new utility standard that requires a complete explanation of the working model that forms the scientific basis of the claimed invention, and that the new standard applied by the Office is improper. The Examiner respectfully disagrees. The Office is not asserting a new utility standard, but is asserting an established standard, as indicated above. Furthermore, a complete explanation of the working model is not required. However, given the broad scope of the claim (specifically that "modulates a lipid" *any* effect on *any* lipid), a fuller explanation is required in order for the claimed method to have a "real world" use. Without any indication of what modulating effect the identified reagent would have on a lipid, further experimentation would be required in order to impart a practical, real world use for the claimed method.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (enablement) it is acknowledged that the claims have been amended such that relate to identifying an agent that inhibits the binding of ligand to HBM and/or Zmax1, thus rendering this aspect of the rejection moot. However, Applicants arguments have not overcome the rejection as a whole. Applicants argue that the claimed invention is a method of identifying an agent that modulates lipid and assert that the specification has disclosed that subjects having the HBM polymorphism have lower triglyceride and VLDL levels and men expressing HBM have a different ration of LDL to HDL ratio, compared to controls. Applicants assert that at the very least one of skill in the art would expect the reagents screened by the method to modulate triglyceride and VLDLs, and,

additionally, one of skill in the art would know to look at the lipid profile of LDL to HDL of a particular reagent using the claimed method. Applicants also argue that there is homology between HBM, Zmax1 and the LDL receptor family and contend that this indicates that HBM and Zmax1 are members of the LDL receptor family. Applicants also argue that Zamx1 binds to ApoE, a lipoprotein and that the presence of the HBM variant is associated with an enhanced lipid profile (decreased triglycerides and VLDL). Applicants also argue that the complexity lipid metabolism and the fact that HBM and Zamx1 may also be involved in pathways not related to lipid metabolism do not detract from their alleged role in modulating lipid regulation. Applicants contend that the Office does not assert that it would take undue experimentation in order to perform the claimed assay and assert that the factor of quantity of experimentation is misapplied. With respect to the Magoori and Fujino references, Applicants appear to concede that Magoori and Fujino do not disclose how LRP5 is involved in lipid regulation by asserting that the exact model of how an invention works does not have to be disclosed and assert that the fact that the exact model of lipid regulation is not fully elucidated is not pertinent to whether the claims have utility. Applicants also disagree with the Office's conclusion that Magoori and Fujino do not teach that LRP5 is directly involved in lipid regulation. Applicants point out that the standard is a preponderance of the evidence, and assert that the specification and the cited art provide evidence that would have led one of skill in the art to conclude that Zmax1 and HBM are involved in lipid regulation. Applicants also disagree with the Office's representation of the references teachings. Applicants also discuss the Zabaglia reference and have submitted a certified translation of the Zabaglia reference. Applicants contend that the Office has selectively chosen the data in order to manufacture support for the Offices' position. Applicants also argue

that LRP5, Zmax1 and HBM genes are variants of each other and assert that LRP5 and Zmax1 are considered wild-type variants and reiterated that HBM is a single amino acid variant that has been associated with high bone mass. Applicants assert that the differences in the protein do not change the action of the protein in various signal cascades. Applicants also discuss the Johnson and Little references and point out that the reference do appear to indicate that the HBM polymorphism is associated with high bone mass.

With respect to Applicants assertion that the specification has disclosed that subjects having the HBM polymorphism have lower triglyceride and VLDL levels and men expressing HBM have a different ratio of LDL to HDL ratio, compared to controls and that at the very least one of skill in the art would expect the reagents screened by the method to modulate triglyceride and VLDLs, it is acknowledged that HBM has been associated with lower triglycerides/VLDL levels and a better LDL:HDL ratio compared to controls. However, the mere association of HBM to these phenotypes does not establish that the claimed method is fully enabled for identifying reagents that modulate a lipid, for the reasons of record. Specifically, The art of record clearly indicates that "modulating a lipid" (which is a very broad limitation) is a complex process that involves the action of many different genes as well as other factors such as diet. Specifically, Ye et al. (2000; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, with respect to plasma lipid levels, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in modulating the plasma lipid

levels. Therefore, Ye teaches that modulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products. Therefore, it is clear that "modulating a lipid" is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and processes. Therefore, the mere association of HBM to a particular lipid profile is not indicative that the claimed method is enabled for the full scope of identifying reagents that modulate lipids. Based on the teachings of Ye, after completion of the claimed method, additional experimentation would required in order establish that the identified reagent actually modulates a lipid.

Additionally, in order for the method to be able to identify molecules that modulate lipid regulation, it is imperative that HBM and Zmax1 are specifically lipid modulation. The specification discloses that HBM and Zmax1 are LDL-receptor family members, based on sequences similarity to known LDL-receptors as well as the association of the HBM polymorphism with a particular lipid profile. There is no disclosure in the specification which indicates either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid modulation. Therefore, additional experimentation is required.

It is noted that all of the art of record has been reviewed as well as applicants' arguments. In view of the totality of the cited art, it is clear that a mere observations that HBM is associated with a particular lipid profile and that Zmax1 binds to ApoE, and the disclosure that HBM and Znmax1 are members of the LDL receptor family of proteins are not sufficient to establish that HBM and Zmax1 are directly involved in modulating lipids, which is required in order for the claimed methods to have utility and to be fully enabled.

With respect to Applicants argument that the complexity lipid metabolism and the fact that HBM and Zamx1 may also be involved in pathways not related to lipid metabolism do not detract from their alleged role in modulating lipid regulation, the Examiner respectfully disagrees. The fact that HBM and Zmax1 may be involved in pathways unrelated to lipid modulation in combination with the fact that lipid regulation is a complex process involving many different factors indicates that HBM and Zmax1 may be functionally unrelated to lipid modulation, which is clearly indicative that additional experimentation would be required in order to fully enable the claimed invention.

With respect to Applicants arguments regarding the indicated references, Applicants arguments have been fully considered but are not persuasive. The issues of the indicated references were previously addressed and Applicants arguments are not sufficient to overcome the rejection. The references do not establish that the claimed methods would be fully enabled for identifying lipid modulators for the reasons of record as well as the reasons indicated herein. In summary, the claims have been rejected for not being fully enabled because the specification, as well as the art at the time of filing, does not establish that HBM and Zmax1 can be used to reliable identify lipid modulators without performing an undue amount of additional experimentation.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Anne-Marie Falk

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PRIMARY EXAMINER